

Comment on “Steady-state fluctuations of a genetic feedback loop: an exact solution” [J. Chem. Phys. 137, 035104 (2012).]

Guilherme C.P. Innocentini,¹ Alexandre F. Ramos,² and José Eduardo M. Hornos^{3, a)}

¹⁾*Instituto de Matemática e Estatística, Universidade de São Paulo, Caixa Postal 66281, BR-05315-970 São Paulo, S.P., Brazil*

²⁾*Escola de Artes, Ciências e Humanidades, Universidade de São Paulo, Av. Arlindo Béttio, 1000 CEP 03828-000, São Paulo, SP, Brazil*

³⁾*Instituto de Física de São Carlos, Universidade de São Paulo, Caixa Postal 369, BR-13560-970 São Carlos, S.P., Brazil*

In the commented article modifications of the Spin-Boson Model¹, for a binary self-regulating gene, have been proposed. The new master equations allow two different decay rates for free and bound proteins. It also presents a vigorous critique of the article ‘Self-Regulated gene: an exact solution’² and ‘subsequent publications’^{3–6} reducing the finding of exact solutions for the spin model to “just a claim” of the authors and not as a rigorous result with the strength of a theorem.

Despite the main criticism on the mentioned solutions they are really dueling with corrections to the master equations for stochastic gene expression viewed as a many-body problem. In the section dedicated to our article the exactness of our solution is questioned again and even a demon, perhaps ironically, is used to explain one of the approximations made in the formulation of the Spin Boson Model. The task of the demon is the instantaneous replacement of the decaying bound protein to the cytoplasm and the inexactness of the solution is a heritage of the inexactness of the master equations. The confusion between solutions and equations goes until the end of the paper when they state that ‘our’ equations (meaning the Spin Boson Formalism) and theirs are dedicated to the same problem so one of them must be wrong! Either demons or exact equations do not belong to science but the concept of an exact solution for a differential equation is well defined and exhaustively studied in the field of symmetries and integrable systems. Indeed we have been able to show that solubility of the Spin Boson models has underlying symmetries^{3,6}.

Both equations contains several approximations and are very far from biological details even if we considered a simpler induced transcription in E.Coli. The most important limitation of this class of models is the bypassing of the whole transcription process and even a demon is not able to take the information from the DNA, to build the mRNA and translate it in the ribosomes instantaneously, putting back the protein to control the promoter site. Using the terminology introduced by the authors, science has a plenty of demons and the crucial question is the selection of proper approximations needed to predict and to explain the experiments successfully.

In section V the authors presents a section named:

Numerical Validation of The Exact Solution which completes the confusion. Exact solutions, by definition, don’t need a numerical check and are verified analytically. A solution can not be validated by a numerical simulation or even by an experiment: the occurrence of an agreement only says that the equations are not wrong. In contrary, the exact analytical solutions are frequently used to validate numerical simulations, stability of algorithms and so on.

The authors report the finding of an exact solution for the steady-state genetic feedback loop. Examining the paper we could not find a complete exact solution for the model as announced in the title, but just half of the work has been carried out. In fact, they present an exact general solution for one probability distribution named $G_1(z)$ but they fail to get the other one $G_0(z)$ in closed form as they recognize explicitly. Mentioning that the equation obtained for this component is not of Riemann type they only write a first order differential equation for it, complaining that “It is difficult to extract an explicit solution for $G_0(z)$ by integrating this equation”. If the authors have read Refs.^{2,6} carefully, would learn that these equations are not Riemann type but from another family, the Heun equations, and therefore, still integrable.

Consequently the normalization constant is not calculated obstructing the analyticity of the whole model. The underlying reason is that “apparently unknown” integrals are needed to obtain the exact solution. They also recognize that they cannot calculate the fluctuations as a function of the parameters of the model, without the numerical computation of the normalization, but only the fluctuation divided by the mean value, also known as the Fano factor.

The use the generating function technique replaces the traditional recursive form of the master equations by partial differential equations with the introduction of the complex functions $G_0(z) = \sum_{n=0}^{\infty} P_0(n)z^n$ and $G_1(z) = \sum_{n=0}^{\infty} P_1(n)z^n$, where n is the stochastic variable, the number of protein molecules, and $P_0(n)$ and $P_1(n)$ are the usual probabilities. At steady state limit the problem reduces to the solution of the system

$$(z - 1)(\rho_u G_0 - G'_0) + (\theta + \sigma_u z)G_1 - \sigma_b z G'_0 = 0, \quad (1)$$

$$(z - 1)(\rho_b G_1 - G'_1) - (\theta + \sigma_u)G_1 + \sigma_b G'_0 = 0. \quad (2)$$

^{a)}Electronic mail: hornos@ifsc.usp.br

$G_1(z)$ may be written as a product between $Ae^{\rho_b(z-1)}$ and the KummerM function $M(\alpha, \beta, w)$, where

$$\alpha = \theta + \sigma_u \frac{\rho_u - \rho_b}{\rho_u - \rho_b - \rho_b \sigma_b}, \quad (3)$$

$$\beta = 1 + \theta + \frac{\sigma_u + \sigma_b(\sigma_u + \rho_u)}{(1 + \sigma_b)^3}, \quad (4)$$

$$w = (\rho_u - \rho_b - \rho_b \sigma_b) \frac{(1 + \sigma_b)z - 1}{(1 + \sigma_b)^2}. \quad (5)$$

We obtain $G_0(z)$ taking linear combinations of the Eqs. (1) and (2):

$$G_0(z) = Ae^{\rho_b(z-1)} \times \left[\frac{1 + \sigma_b}{\sigma_b} \frac{\alpha}{\rho_u} M(\alpha + 1, \beta, w) + \frac{\theta - \alpha}{\rho_u - \rho_b} M(\alpha, \beta, w) \right], \quad (6)$$

as we can verify by direct substitution. Normalization constant A follows from probability conservation as usual and gives to this model same status of that presented by Hornos *et.al.*

Throughout their article the authors explain why our solutions are not exact and theirs are. The reason is that the equations for the spin boson model of Ref.² are not exact, some terms are missing and others are “non-physical”. Consequently our solution is not exact because our equations are not exact. In contra-position their stochastic equations are “exact” and therefore the partial solution they presented are exact.

Even though we are not claiming that our solutions have the same status, let us consider the exact solution for the Schrödinger equation for hydrogen and numerical solutions for the Helium atom. Of course the Schrödinger equation for an electron in the Coulomb field is not exact and unphysical if one want to use those terms. The Coulomb potential depends only on the radius, relativistic terms are missing, quantized electromagnetic field is absent. The use of the space dependent potential violates special relativity and is incompatible with Maxwell equations that are Lorentz invariant. An static potential between to charges is only possible if we assume the existence of a “daemon” which instantaneously tells one charge that the other did a small movement. Following their reasoning the hydrogenic solution in terms of spherical harmonics and Laguerre functions are not exact! Of course this is not the case for two reasons:(i) there are no exact equations in Science and (ii) we consider an exact solution for a given equation if we can solve it analytically in a closed form. Even if one relax the definition of exact solution in closed form to numerical evaluation of exact solution, *i.e.* numerical solutions to a target equation, without approximations, calculated with desired precision, one cannot call the exact solutions presented at Refs.^{2,6} as just a claim or use quotes to diminish the value of the calculation. In practice the exact solutions are powerful because they allow any calculation

and the study of the parametric equation of one model. Furthermore, approximations and physical intuition are also easier if we have exact solutions.

The stochastic equations proposed in their article are different from the spin boson ones. Indeed there is no parameter that can be used to obtain rigorously one set of equations from the other. Both are unphysical and approximated. The transcription process, the ribosomes, tRNA’s and the amplification of the protein number by repeated translation of one mRNA have been eliminated in both models which is a radical oversimplification of any protein synthesis process. Even in the transcription of the *lac* operon of E.Coli controlled by the *Lac Repressor*, the comparison with experiments requires two stochastic processes⁷. In the compared models another daemon is required, it carries one mRNA on a hand and the ribosomes on the other, translating instantaneously and repeatedly the anticodon information.

The proposed model is welcome and has some interesting modifications as claimed by the authors. The instantaneous reposition of protein to the binding mode is avoided and the protein degradation when the protein is bound is taken into account, even though a new parameter must be included. However, the strict interpretation of both models, and, consequently, of the parameters, is not promising. The transcription and translation processes considered here have several time scales. For example, the free proteins degradation, the bacterial division time, the mRNA degradation time that usually is much smaller than the protein degradation, the discrepancy between mRNA and protein number of molecules by more than an order of magnitude in E.Coli⁸. This means that we must have an extra guiding principle to perform a physical analysis and the best one are the available experiments. The critique present here do not diminishes the importance of their proposal which can be considered an alternative for negative self-regulation.

¹M. Sasai and P. G. Wolynes. Stochastic gene expression as a many-body problem. *Proc Natl Acad Sci U S A*, 100(5):2374–9, 2003.

²J. E. Hornos, D. Schultz, G. C. Innocentini, J. Wang, A. M. Walczak, J. N. Onuchic, and P. G. Wolynes. Self-regulating gene: an exact solution. *Phys Rev E Stat Nonlin Soft Matter Phys*, 72(5 Pt 1):051907, 2005.

³A. F. Ramos, J. E. M. Hornos. Symmetry and stochastic gene regulation. *Phys Rev Lett*, 99(10):108103, 2007.

⁴D. Schultz, J. N. Onuchic, P. G. Wolynes Understanding stochastic simulations of the smallest genetic networks. *J. Chem. Phys.*, 126, 1–11, 2007.

⁵A. F. Ramos and G. C. P. Innocentini and F. M. Forger and J. E. M. Hornos. Symmetry in biology: from genetic code to stochastic gene regulation. *IET Systems Biology*, 4:311–329, 2010.

⁶A. F. Ramos, G. C. P. Innocentini, J. E. M. Hornos. Exact time-dependent solutions for a self-regulating gene. *Physical Review E*, 83:062902, 2011.

⁷M. Thattai and A. van Oudenaarden. Intrinsic noise in gene regulatory networks. *Proc Natl Acad Sci USA*, 98, 8614–8619, 2001.

⁸L. Cai, N. Friedman, X.S. Xie Stochastic protein expression in individual cells at the single molecule level. *Nature*, 440, 358–362, 2006.